(19) JAPANESE PATENT OFFICE (JP)

(12) Official Gazette for Unexamined Patent Applications (A)

(11) Japanese Unexamined Patent Application (Kokai) No. Hei 1-93519

(43) Disclosure Date: 12 April 1989

(51) Int.Cl.[4]	Ident. Symbols	Internal Office Nos.
A 61 K 7/42		6971-4C
7/00		X-7306-4C
		C-7306-4C
31/195	ADA	7330-4C
// C 07 C 101/04		

Request for Examination: Not yet requested Number of Inventions: 1 (Total of 9 pages)

(54) Title of the Invention: Antipigmentation Agent for External Use

(21) Application No.: Sho 62-249134

(22) Application Date: 2 October 1987

(72) Inventor: Nobuhiko Azuma
3-2-6 Kofu, Fujiidera-shi, Osaka-fu

(72) Inventor: Keisuke Nakajima
c/o Research Laboratories, Shiseido Co., Ltd.
1050 Nitsuba-cho, Kohoku-ku, Yokohama-shi,
Kanagawa-ken

(72) Inventor: Kaoru Hakamata
c/o Shiseido Company, Ltd.
5-5 Ginza 7-chome, Chuo-ku, Tokyo-to

(72) Inventor: Emiko Takasu
c/o Shiseido Company, Ltd.
5-5 Ginza 7-chome, Chuo-ku, Tokyo-to

(71) Applicant: Shiseido Company, Ltd.
5-5 Ginza 7-chome, Chuo-ku, Tokyo-to

(71) Applicant: Nobuhiko Azuma
3-2-6 Kofu, Fujiidera-shi, Osaka-fu

SPECIFICATION

1. Title of the Invention

Antipigmentation Agent for External Use

2. Claim

(1) An antipigmentation agent for external use characterized in that tranexamic acid, its salts or mixtures thereof are contained in it.

3. Detailed Description of the Invention

[Field of Industrial Use]

This invention relates to a novel antipigmentation agent for external use. In greater detail, it relates to an anti-pigmentation agent for external use of high safety in which tranexamic acid, salts thereof or mixtures thereof are the effective constituents.

[Prior Art]

Chromatopectic conditions include deposition of pigment after sunburn, freckles, liver spots, melasma, pigmented aging spots, petal-shaped pigment deposition, sunlight keratoderma, pigmented birthmarks, large birthmarks and berlock dermatitis. There are many aspects of the mechanism of occurrence of these forms of pigment deposition that are not yet clear. In general, it is thought that there is abnormal deposition of melanin in the skin due to genetic factors, hormonal abnormalities, skin irritation such as irritation by the ultraviolet rays of sunlight and chemical substances and darkening due to allergic contact dermatitis.

The methods that are generally used for the treatment of these types of pigmentation conditions are oral use of substances that inhibit melanin production, for example, vitamin C and glutathione, and topical use of vitamin C and cysteine. In the United States and Europe, hydroquinone preparations are used as medicinal drug products.

In addition, among natural drugs, extracts of angelica root, **kyokatsu** [*Notopterygium incisum*], **senkyu** [*Ligisticum* root], aloe, pollen, gardenia, mulberry root bark, cimicifuga, soybeans, arrowroot and gourds (Japanese Patent Application Early Disclosure No. 56-92208 [1981], Japanese Patent Application Early Disclosure No. 50-135236 [1975] and Japanese Patent Application Early Disclosure No. 57-77610 [1982] are known as antipigmentation agents. In addition, in relation to vitamin C, 3-0-glucosyl-L-ascorbic acid, N-acyl amino acid ester ascorbic acid, 3-0-monoester ascorbic acid, and hydroxypropiophenol ascorbic acid (Japanese Patent Application Early Disclosure No. 59-27825 [1984], Japanese Patent Application Early Disclosure No. 56-135411 [1981], Japanese Patent Application Early Disclosure No. 56-161314 [1981], and Japanese Patent Application Early Disclosure No. 51-101138 [1976]; in relation to kojic acid (Japanese Patent Application Early Disclosure No. 53-3538 [1978], Japanese Patent Application Early Disclosure No. 53-6432 [1978], Japanese Patent Application Early Disclosure No. 54-92632 [1979], Japanese Patent Application Early Disclosure No. 56-7710 [1981], Japanese Patent Application Early Disclosure No. 56-79616 [1981], and Japanese Patent Application Early Disclosure No. 59-33207 [1984]); in addition, pantethine, pantetheine and derivatives thereof (Japanese Patent Application Early Disclosure No. 56-73012 [1981], Japanese Patent Application Early Disclosure No. 57-74052 [1982], Japanese Patent Application Early Disclosure No. 58-134022 [1983] and Japanese Patent Application Early Disclosure No. 59-36606 [1984]); hydroquinone fatty acid esters (Japanese Patent Application Early Disclosure No. 57-145803 [1982] and Japanese Patent Application Early Disclosure No. 58-154507 [1983]); and dicarboxylic acid esters (Japanese Patent Application Early Disclosure No. 58-103319 [1983]) are known. In addition, oral administration of tranexamic acid is known to be effective in the treatment of liver spots (Nishi Nihon Hifu [Nishi Nihon Journal of Dermatology], 47, 6, 1101-1104).

Of these drug preparations, there are problems of stability with ascorbic acid preparations. In systems containing water, this is a cause of changes in color and changes in odor. Thiol compounds such as glutathione and cysteine have strong unpleasant odors and are readily oxidized and are thus to be avoided in the comounding of topical preparations. Moreover, the effect of removing hydroquinone from these compounds occurs extremely slowly, for which reason their effect is insufficient.

Although an effect is found with hydroquinone, it causes sensitization. Because it is too strongly irritating to the skin of Japanese people and because allergic contact dermatitis occurs as a side effect, its use in Japan is limited. In addition, its preparations are unstable. Accordingly, mono-esterification of high fatty acids was attempted in order to improve their stability. However, because these esters are decomposed by hydrolases in the body, it is difficult to say that they are safe. On the other hand, treatment by oral administration of tranexamic acid is particularly effective for liver spots. Effects on freckles and other pigment deposition conditions are infrequent. In addition, on oral administration, tranexamic acid acts on the entire body, for which reason it cannot always be said to be safe.

[Problems the Invention is Intended to Solve]

In view of these circumstances, the inventors conducted intensive research for the purpose of obtaining a drug preparation that would be very safe and that would have superior antipigmentation effects. As the result, it was discovered that tranexamic acid, which has antiplasmin action, or its salts, exhibited sufficient antipigmentation effects and that it was extremely safe. This invention was perfected on the basis of this finding.

[Means for Solving the Problems]

Specifically, this invention is in essence an antipigmentation agent for external use in which tranexamic acid, its salts or mixtures thereof are the effective constituents.

We shall now describe this invention in detail.

The tranexamic acid and salts thereof that are used in this invention are generally used as antiplasmin agents and it is known that as components for use in cosmetics they are characterized in being of high safety (Japanese Patent Application Early Disclosure No. 42-36980 [1967]. Methods of manufacture are found in Japanese Patent No. 240611, No. 242664, No. 480411 and No. 488168. The melting point of tranexamic acid is 262 to 267°C (decomposition). It consists of white crystals or powder and is odorless and tasteless.

Tranexamic acid salts are salts that are commonly used and include salts of metals such as Mg, Ca and K, phosphates, hydrochlorides, hydrobromides and sulfates. Derivatives include vitamin esters such as vitamin A acid esters, vitamin A esters, vitamin E esters, vitamin C esters and vitamin D esters, phenyl esters and N,N-maleoylaminotranexamic acid. However, they are not limited to these substances.

The term pigment deposition condition used here refers to freckles, liver spots, melasma, pigmented aging spots, petal-shaped pigment deposition, sunlight keratoderma, pigmented birthmarks, deposition of pigment after sunburn, large birthmarks and berlock dermatitis. In addition, it refers to pathological deposition of pigment in the body or to pigment deposition conditions in which similar symptoms are exhibited. Topical agents comprised of tranexamic acid, its salts or mixtures thereof are efficacious in many types of pigment deposition conditions.

(Toxicological Properties]

Next, we shall describe the toxicological properties of this substance.

(1) Acute toxicity

Acute toxicity was studied by various routes of administration using Wistar rats and ICR-JCL mice. For oral administration or transcutaneous administration the substance was dissolved in distilled water. For other forms of administration, the substance was dissolved in physiological saline solution. The preparations were adjusted to specified quantities and were administered using a stomach probe or a syringe.

Observation for toxic symptoms was continued after administration, the death rates over time up to 7 days and the LD_{50} values were found. The surviving animals and the animals that died were autopsied and findings were obtained. LD_{50} were calculated by the Litchfield-Wilcoxon graphic calculation method.

It was found that high LD_{50} were exhibited for this substance in all administrations and it was found to be safe as a medicinal drug.

Table 1

Route of administration	LD50 value (95% confidence limit)	
	Rats male – female	Mice male - female
Oral	> 10 g/Kg	> 10 g/Kg
Transcutaneous	> 10 g/Kg	> 10 g/Kg
Subcutaneous	5 g/Kg	5 g/Kg
Intravenous	1 g/Kg	1 g/Kg

No problematic changes were found with respect to general symptoms, body weight, amounts of feed and water consumption and autopsy findings.

(2) Sensitization

The tests were performed in accordance with the maximization test method of Magnusson and Kligman (Magnusson B. and Kligman, A.M.). Specifically, the method was as follows.

(1) Induction of sensitization

Twenty guinea pigs were prepared, with 10 being used for sensitization induction and 10 being used as controls during sensitization. An area of 4 × 6 cm in the vicinity of the scapula of the guinea pig was shaved off with a razor and the three pairs of skin injections a, b and c indicated below were made at the same time on the left and right sides, with the center line as the control.

a. Left and right: Amounts of 0.5 ml f FCA for a total of 0.1 ml in two places.

b. Left and right: 0.05 ml test material, in two places (aqueous solution containing 10% test material)

c. Left and right: 0.05 ml test material emulsified in FCA, in two places

One week after the intradermal injection, the vicinity of the scapula was again shaved, vaseline containing 10% of sodium lauryl sulfate was applied to bring about severe inflammation. Sensitization was intensified as a result of this treatment. Test material was then applied to this site with an occlusive dressing.

(2) Stimulation (Challenge)

On day 21 after induction of sensitization, areas of 5 × 5 cm on the lateral abdominal region of the guinea pigs in the sensitization treatment group and the control group were shaved off with a razor, the test material was applied in a suitable solvent and an occlusive dressing was applied for 24 hours. The same procedure was used in the control group.

(3) Evaluation

i	No change seen with unaided eye	0
ii	Mild or very slight erythema	1
iii	Moderate degree of erythema	2
iv	High degree of erythema and edema	3

(4) Results

No sensitization responses were seen in any of the guinea pigs. This indicates that this substance is safe even when it is used transcutaneously for a long period.

(Pharmacological effects)

(1) Antipigmentation effect and side effects

Eight MOP-treated phototoxic pigmentation Weiser Maple guineapigs were used. Amounts of 50 μl test sample were applied once a day for 8 weeks to an area of approximately 4 cm^2 on the shaved backs; the antipigmentation effect and the degree of intensification of pigment that appeared as a side effect were rated by a four-point evaluation method (+: depigmentation effect; -: side effect). The samples used were 5% hydroquinone (PG solution) and 5% tranexamic acid PG suspension.

Table 2. Rating. Depigmentation Effect and Pigment Deposition

	Evaluation	Evaluation score	Visual evaluation
Antipigmentation effect	+	3	Became white
	±	2	Became somewhat white
	- ~ ±	1	Became very slightly white
	-	0	No change
Side effects – pigment intensification	-	0	No change
	- ~ ±	-1	Became somewhat black
	±	-2	Became black
	+	-3	Became clearly black

Table 3. Results

Drug preparation	Number with daily application (weeks)							
	1	2	3	4	5	6	7	8
Hydroquinone	0.4	0.7	1.2	0.8	0.3	0.2	-0.5	-0.8
This product	0.6	1.5	2.0	2.1	2.0	2.1	2.0	1.9

With hydroquinone, pigment deposition was found as a side effect resulting from its long-term continued use. By contrast, tranexamic acid exhibited an excellent depigmentation effect and no side effects occurred as a result of its long-term continued use.

(Preparation making)

Next, we shall describe making preparations for the purpose of using tranexamic acid, salts thereof or mixtures thereof as antipigmentation topical agent.

The tranexamic acid, salts thereof or mixtures thereof of this invention are provided for use as mixtures of the base compositions and other drug preparations that are permissible in drug preparation. When tranexamic acid, its salts or mixtures thereof are used in combination with ultraviolet absorbents with the objective of blocking ultraviolet rays, they are effective in preventing sunburn, promoting recovery from sunburn and in the prevention and treatment of pigment deposition conditions.

The above-described base compositions contain excipients such as lactose, starch, calcium carbonate, magnesium aluminate metasilicate, magnesium aluminum hydroxide, calcium hydrogen phosphate, sugar, lactose, aluminum silicate and microcrystalline cellulose, binders such as carboxymethyl cellulose, polyvinyl pyrrolidone, gum arabic, gelatin, sodium alginate and hydroxypropyl starch; lubricants such as talc, magnesium stearate and zinc stearate, humectants such as glycerol, propylene glycol and sorbitol, disintegration agents such as agar, silicic anhydride and carboxymethyl-cellulose calcium, and, in addition, surfactants, buffering agents, preservatives, fragrances, pigments, oleaginous components, dyes, water, alcohol, thickeners, putrefaction inhibitors, antioxidants and chelating agents. They may be used individually or in mixtures of two or more. However, there are no limitations on them.

The above-described drug preparations can include skin nutrients, enzymes and existing beautifying agents.

For example, they can include iodotyrosine and derivatives thereof, amino acids such as methionine, lysine and serine and derivatives thereof, vitamin preparations such as vitamin A, pantothenic acid, biotin, vitamin B_1, vitamin B_2, nicotinic acid, vitamin C, vitamin E, vitamin F and derivatives thereof, enzymes and hormones such as female hormones, pituitary hormone and phosphorylase, antiinflammatory agents such as allantoin, salicylic acid, urea, coix seed, various plant extracts, glycyrrhizin, glycyrrhetin and acids and derivatives thereof, and, in addition, inositol, orotic acid, thioctic acid, chondroitin sulfate and hyaluronic acid. However, they are not limited to these substances.

The above-described ultraviolet absorbents can be the benzoic acid derivatives such as para-aminobenzoic acid (hereinafter abbreviated as PABA), PABA monoglycerol diesters, N,N-dipropoxy PABA ethyl esters, N,N-dimethyl PABA ethyl esters, N,N-dimethyl PABA butyl esters, N,N-dimethyl PABA amyl esters and N.N-dimethyl PABA octyl esters. Anthranilic acid systems include homomenthyl-N-acetyl anthranilate. Salicylic acid derivatives include amyl salicylate, menthyl salicylate, homomenthyl salicylate, octyl salicylate, phenyl salicylate, benzyl salicylate and p-isopropanol phenyl salicylate. Cinnamic acid derivatives include octyl cinnamate, ethyl-4-isopropyl cinnamate, methyl-2,5-diisopropyl cinnamate, ethyl-2,4-diisopropyl cinnamate, methyl-2,4-diisopropyl cinnamate, propyl-p-methoxycinnamate, isopropyl-p-methoxycinnamate, isoamyl-p-methoxycinnamate, octyl methoxycinnamate, 2-ethoxyethyl-p-cinnamate, cyclohexyl-p-methoxycinnamate, ethyl-α-cyano-β-phenyl cinnamate, 2-ethylhexyl-α-cyano-β-phenyl cinnamate and glycyrrhizin-2-ethylhexanoyldiparamethoxycinnamate. Benzophenone derivatives include 2,4-dihydroxybenzophenone, 2,2'-dihydroxy-4-methoxybenzophenone, 2,2'-dihydroxy-4,4'-dimethoxybenzophenone, 2,2',4,4'-tetrahydroxybenzophenone, 2-hydroxy-4-methoxybenzophenone, 2-hydroxy-4-methoxy-4'-methoxybenzophenone, 2-hydroxy-4-methoxybenzophenone-5-sulfonate, 4-phenylbenzophenone, 2-ethylhexyl-4'-phenylbenzophenone-2-carboxylate, 2-hydroxy-4-n-octoxyphenylbenzone and 4-hydroxy-3-carboxybenzophenone. Further, ultraviolet absorbents include 3-(4'-methylbenzylidene)-d,l-camphor, 3-benzylidene-d,l-camphor, urocanic acid, urocanic acid ethyl ester, 2-phenyl-5-methylphenyl-benzotriazole, 2,2'-hydroxy-5-methylphenyl-benzotriazole, 2-(2'-hydroxy-5'-

Methylphenyl-benzotriazole, dibenzaladine, dianisoylmethane, 4-tetrakis-4'-butyl-dibenzoylmethane, 5-(3,3'-dimethyl-2-norbornylidene-3-pentan-2-one and benzal phthalide.

However, these substances are not limited to those listed above.

The type of preparation in this invention can be any desired type that is used for ordinary medicinal drug products, products other than medicinal drugs and cosmetics as long as it is suited to the obtaining of drug effects as an antipigmentation agent for topical use. For example, it can be a solution for topical use such as lotion, a liniment, an aqueous solution or an emulsion, a solid topical agent such as a powder or soluble tablet, a semisolid agent for topical use such as a cream, a coating film, an ointment, a paste or a gel or a soap. Effects can also be obtained with agents for oral use and injected agents and any method may be used in combination.

The tranexamic acid, which is the active constituent in the antipigmentation agent for topical use of this invention, its salts or mixtures thereof, should be added in amounts of 0.0001 to 50 % by weight, preferably, 0.01 to 10 % by weight, and, more preferably, 0.1 to 1 % by weight. When the content is 50 % by weight, the effect is sufficient and no intensification of the effect is seen even if it is added in greater amounts. With less than 0.0001%, a sufficient effect is not obtained.

(Administration Method and Doses)

The antipigmentation agent for topical use of this invention is primarily applied directly to the affected site and passes through the skin. It can also be administered by other methods such as oral administration, subcutaneous injection, intravenous administration and intramuscular injection.

The administration dose of the antipigmentation agent for topical use of this invention is affected by age, individual differences and symptoms. There are also instances in which doses outside the range indicated below are administered depending on the circumstances and depending on the objective of use. On topical use, tranexamic acid, its salts or mixtures thereof are applied several times a day to the diseased site in amounts of 0.005 to 20 mg/cm^2. However, the salts are not limited to this amount.

(Action)

Next, actual use tests were performed using topical agents to which tranexamic acid had been added in order to clarify the antipigmentation effect of the tranexamic acid, its salts or mixtures thereof of this invention.

(Test method) A panel was constituted of 50 subjects having pigment deposition conditions on their faces. Half of them, or 25 subjects, were given the preparation of Working Example 1, and the other half, or 25 subjects, were used as comparison cases, being given a preparation from which the tranexamic acid of Working Example 1 was omitted and in which water was substituted for it. These preparations were applied to the face 2 to 3 times a day. After 3 months of continued use, evaluations of the pigmentation lightening effect were made by a physician using the unaided eye.

Table 4. Results

Cases / General degree of improvement		Liver spots	Freckles	Deposition of pigment due to aging	Other conditions	Totals
Working Example 1: tranexamic acid added	Considerable improvement	5	4	2	0	11 persons
	Some improvement	2	5	2	1	8 persons
	No change	1	1	3	1	6 persons
	Aggravation	0	0	0	0	0 persons
	Total number of cases	8	8	7	2	25 persons
Comparative Example 1: tranexamic acid not added	Considerable improvement	0	0	0	0	0 persons
	Some improvement	2	1	1	1	4 persons
	No change	6	7	6	2	21 persons
	Aggravation	0	0	0	0	0 persons
	Total number of cases	8	8	7	2	25 persons

As should be evident from the above-described results, it was confirmed that an antiipigmentation agent containing 2.5 % by weight of tranexamic acid had superior effects with an efficacy rate of 76.0%.

This agent is an antipigmentation prevention and treatment agent that is markedly efficacious for not only liver spots but also many types of pigment deposition conditions, that can tolerate long-term use and that is of high safety. It does not have side effects and is effective in preventing sunburn and in promoting recovery from it. It is therefore suitable for use as a cosmetic.

[Working Examples]

We shall now describe this invention in greater detail by means of Working Examples. This invention is not limited to them.

The quantities used are given in % by weight.

(Working Example 1)

	% by weight
Stearic acid	6.0
Sorbitan monostearic acid ester	2.0
Polyoxyethylene (20 mol) sorbitan monostearic acid ester	1.5
Propylene glycol	10.0
Tranexamic acid	2.5
Preservative – antioxidant	suitable quantity
Fragrances	suitable quantity
Ion exchange water	remainder

(Preparation method)

Tranexamic acid and propylene glycol were added to the ion exchange water and the mixture was heated and maintained at 70°C (aqueous phase). The other components were mixed, heated and fused and maintained at 70°C (oily phase). The oily phase was added to the aqueous phase and a preliminary emulsification was performed. The mixture was then emulsified to a homogeneous state with a homomixer, after which the product was cooled to 30°C while being thoroughly stirred.

(Working Example 2)

	% by weight
95% ethanol	10.0
Polyoxyethylene (15 mol) oleyl alcohol ether	2.0
Olive oil	2.0
Preservative	suitable quantity
Fragrances	suitable quantity
Polyvinyl alcohol	12.0
Glycerol	3.0
Polyethylene glycol 1500	1.0
Tranexamic acid	1.0
Ion exchange water	remainder

(Preparation method)

The aqueous phase was adjusted to 80°C and cooled to 50°C. The alcohol phase from which olive oil had been removed was adjusted to room temperature and was added to the aqueous phase, after which the olive oil was added and mixed to a homogeneous state and then cooled.

(Working Example 3)

	% by weight
Stearyl alcohol	7.0
Stearic acid	2.0
Hydrogenated lanolin	2.0
Squalane	5.0
2-octyl dodecyl alcohol	6.0
Polyoxyethylene (25 mol) cetyl alcohol ether	3.0
Glycerol monostearic acid ester	2.0

Tranexamic acid vitamin E ester	0.25
Propylene glycol	5.0
Preservative – antioxidant	suitable quantity
Fragrances	suitable quantity
Ionized water	remainder

(Preparation method)

The tranexamic acid – vitamin E ester and propylene glycol were added to the ion exchange water, heated and maintained at 70°C (aqueous phase). The other components were mixed, heated and fused and maintained at 70°C (oily phase). The oily phase was added to the aqueous phase and preliminary emulsification was performed. The mixture was then emulsified to a homogeneous state with a homomixer, after which the product was cooled to 30°C while being thoroughly stirred.

(Working Example 4)

	% by weight
Solid paraffin	5.0
Beeswax	10.0
Vaseline	15.0
Liquid paraffin	41.0
Glycerol monostearic acid ester	2.0
Polyoxyethylene (20 mol) sorbitan monolauric acid ester	2.0
Soap powder	0.1
Tranexamic acid	10.0
Borax	0.2
Preservative – antioxidant	suitable quantity
Fragrances	suitable quantity
Ion exchange water	remainder

(Preparation method)

The tranexamic acid, soap powder and borax were added to the ion exchange water, dissolved by heating and maintained at 70°C (aqueous phase). The other components were mixed, dissolved by heating and maintained at 70°C (oily phase). The oily phase was gradually added to the aqueous phase as the mixture was being stirred and a reaction occurred. After the reaction was completed, the mixture was then emulsified to a homogeneous state with a homomixer. After emulsification, the product was cooled to 30°C with vigorous stirring.

(Working Example 5)

	% by weight
Stearic acid	2.5
Cetyl alcohol	2.0
Vaseline	5.0
Liquid paraffin	10.0
Polyoxyethylene (10 mol) monooleic acid ester	2.0
Polyethylene glycol 1500	3.0
Triethanolamine	1.0
Tranexamic acid	0.01
Preservative – antioxidant	suitable quantity
Fragrances	suitable quantity
Ion exchange water	remainder

(Preparation method)

The tranexamic acid, polyethylene glycol 1500 and triethanolamine were added to the ion exchange water, dissolved by heating and maintained at 70°C (aqueous phase). The other components were mixed, dissolved by heating and maintained at 70°C (oily phase). The oily phase was added to the aqueous phase and a preliminary emulsification was performed. The mixture was then emulsified to a homogeneous state with a homomixer, after which the product was cooled to 30°C with vigorous stirring.

(Working Example 6)

	% by weight
Stearic acid	1.5
Cetyl alcohol	0.5
Beeswax	2.0
Polyoxyethylene (20 mol) monooleic acid ester	1.0
Glycerol monostearic acid ester	1.0
Tranexamic acid	0.0001
Quince seed extract solution (5% aqueous solution)	20.0
Propylene glycol	5.0
Ethyl alcohol	10.0

Preservative – antioxidant	suitable quantity
Fragrances	suitable quantity
Ion exchange water	remainder

(Preparation method)

The tranexamic acid and propylene glycol were added to the ion exchange water, dissolved by heating and maintained at 70°C (aqueous phase). The fragrance and ultraviolet ray absorbent were added to the ethyl alcohol and dissolved in it (alcohol phase). The other components except for the quince seed were mixed, dissolved by heating and maintained at 70°C (oily phase). The oily phase was added to the aqueous phase, preliminary emulsification was performed and the mixture was emulsified to a homogeneous state.

The alcohol phase and the quince seed extract solution were added to the product as it was being stirred. It was then cooled to 30°C with stirring.

(Working Example 7)

	% by weight
Microcrystalline wax	1.5
Beeswax	2.0
Lanolin	2.0
Liquid paraffin	20.0
Squalane	10.0
Sorbitan sesquioleic acid ester	4.0
Polyoxyethylene (20 mol) sorbitan monooleic acid ester	4.0
Magnesium tranexamate	0.5
Preservative – antioxidant	suitable quantity
Fragrances	suitable quantity
Ion exchange water	remainder

(Preparation method)

The tranexamic acid and propylene glycol were added to the ion exchange water, dissolved by heating and maintained at 70°C (aqueous phase). The other components were mixed, dissolved by heating and maintained at 70°C (oily phase). The aqueous phase was gradually added to the oily phase as it was being stirred and emulsification was performed to a homogeneous state with a homomixer. After emulsification, the product was cooled to 30°C with vigorous stirring.

(Working Example 8)

	% by weight
95% ethanol	25.0
Polyoxyethylene (40 mol) hardened castor oil ether	4.0
Preservative – antioxidant	suitable quantity
Fragrances	suitable quantity
Dipropylene glycol	15.0
Glycerol	5.0
Sodium hexametaphosphate	suitable quantity
Ultraviolet ray absorbent	suitable quantity
Tranexamic acid	0.2
Ion exchange water	remainder

(Preparation method)

The aqueous phase and the alcohol phase were mixed, after which they were solubilized.

(Working Example 9)

	% by weight
95% ethanol	10.0
Dipropylene glycol	15.0
Ubiquinone-10	0.005
Polyoxyethylene (15 mol) oleyl alcohol	5.0
Carboxyvinyl polymer Brand name: Carbopl 941)	1.0
Tranexamic acid phenyl ester	0.4
Sodium hydroxide	0.15
L-arginine	0.1
Ultraviolet ray absorbent	suitable quantity
Preservative – antioxidant	suitable quantity
Fragrances	suitable quantity
Ion exchange water	remainder

(Preparation method)

The Carbopol 941 and tranexamic acid phenyl ester were dissolved to a homogeneous state in the ion exchange water. Separately, the dipropylene glycol ether and the other components were dissolved in 95% ethanol and the solution was added to the aqueous phase. It was then neutralized with sodium hydroxide and L-arginine and thickened.

(Working Example 10)

	% by weight
Stearic acid	5.0
Stearyl alcohol	4.0
Ascorbic acid butyl alcohol ester	8.0
Glycerol monostearic acid ester	2.0
Tranexamic acid	2.0
Propylene glycol	20.0
Sodium hydroxide	0.2
Preservative – antioxidant	suitable quantity
Fragrances	suitable quantity
Ion Exchange water	remainder

(Preparation method)

The tranexamic acid, propylene glycol and sodium hydroxide were added to the ion exchange water, dissolved by heating and maintained at 70°C (aqueous phase). The other components were mixed, dissolved by heating and maintained at 70°C (oily phase). The oily phase was gradually added to the aqueous phase. After addition of the total amount was completed, this temperature was maintained for a while and a reaction occurred. The product was then emulsified to a homogeneous state with a homomixer and cooled to 30°C with vigorous stirring.

(Working Example 11)

	% by weight
95% ethanol	2.0
Preservative	suitable quantity
Fragrances	suitable quantity
Pigment	suitable quantity
Olive oil	2.0
Propylene glycol	7.0

Zinc white	25.0
Kaolin	20.0
Calcium tranexamate	0.1
Ion exchange water	remainder

(Preparation method)

The aqueous phase was adjusted to a homogeneous state at room temperature. The alcohol phase without the olive oil was then added to the aqueous phase that had been adjusted to room temperature, after which the olive oil was added and mixed until it was homogeneous.

(Working Example 12)

	% by weight
Kaolin	30.5
Talc	5.0
Zinc white	3.5
Olive oil	2.0
Polyoxyethylene (40 mol) sorbitan monolauryl acid ester	1.0
Propylene glycol	8.0
Fragrances	suitable quantity
Preservative	suitable quantity
Tranexamic acid	50.0

(Preparation method)

All of the components except the powder were dissolved and they were sprayed on to and mixed with the powder component.

The detailed mechanism of action of the antipigmentation effect of the tranexamic acid, its salts or mixtures thereof of this invention is not clear.

However, as described above, by applying the antipigmentation agent for topical use of this invention to sites of pigment deposition on the surface of the skin, said site can be treated and improved. In addition, by applying it to skin darkened after sunburn, recovery from sunburn is promoted and the skin can be restored to its normal color. Moreover, it is of extremely high safety and can be tolerated for long periods. It is therefore suited to the prevention and treatment of pigment deposition.

Applicants: Shiseido Company, Ltd.
Nobuhiko Azuma